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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/679,366	10/07/2003	Wei Liu	031896-7000	5643

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KIRKPATRICK & LOCKHART PRESTON GATES ELLIS LLP
STATE STREET FINANCIAL CENTER
ONE LINCOLN STREET
BOSTON, MA 02111-2950

EXAMINER	
STEADMAN, DAVID J	
ART UNIT	**PAPER NUMBER**
1656	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/679,366	LIU ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2005*.
2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.
  4a) Of the above claim(s) *1-7 and 12-23* is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *8,10 and 11* is/are rejected.
7)☒ Claim(s) *9* is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.
10)☒ The drawing(s) filed on *07 October 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.
  Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
  Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  a)☐ All b)☐ Some * c)☐ None of:
    1.☐ Certified copies of the priority documents have been received.
    2.☐ Certified copies of the priority documents have been received in Application No. _____.
    3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
  * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
  Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413)
  Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :1/7/04, 7/23/04, 2/1/05, 5/24/05, 8/5/05, and 11/2/05 .
Continuation of Attachment(s) 6). Other: Appendix A (sequence alignment).

DETAILED ACTION

Status of the Application

[1] Claims 1-23 are pending in the application.

Election/Restriction

[2] Applicant's election without traverse of Group II, claims 8-11, in the reply filed on 11/30/06, is acknowledged.

[3] Claims 1-7 and 12-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Claim for Domestic Priority

[4] Applicant's claim to domestic priority under 35 U.S.C. 119(e) to US provisional application 60/416,257, filed on 10/7/02, is acknowledged.

Information Disclosure Statement

[5] With the exception of the reference of Straub et al. (cited at p. 7 of the IDS filed on 1/7/04), all references cited in the IDSs filed on 1/7/04, 7/23/04, 2/1/05, 5/24/05, 8/1/05, and 11/2/05 have been considered by the examiner. A copy of Forms PTO-1449 is attached to the instant Office action. The reference of Straub et al. has not been considered as the examiner could not locate a copy of the reference in the application file as require by 37 CFR 1.98(d). Also, while certain other references have been lined through, these references are duplicate citations as noted in the margins of the Form PTO-1449.

Specification/Informalities

[6] The specification and drawings are objected to as Figures 1-11 and 13 disclose that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2), however, the sequences do not comply with the requirements of 37 CFR 1.821 through 1.825. When a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequence identifier ("SEQ ID NO:X") must be used, either in the drawing or in the Brief Description of the Drawings. See MPEP § 2422.02. To be in compliance, applicants should identify nucleotide sequences of at least 10 nucleotides and amino acid sequences of at least 4 amino acids in the specification by a proper sequence identifier, i.e., "SEQ ID NO:" (see MPEP 2422.01). If these sequences have not been listed in the computer readable form and paper copy of the sequence listing, applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d).

[7] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: ---Human myotonic dystrophy kinase-related Cdc42 binding kinase 2 (MRCK2) polypeptide---.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[8] Claim(s) 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 is drawn to a fragment of SEQ ID NO:2 and claim 9 limits the fragment as recited in claim 8 to consisting of SEQ ID NO:2. According to Stedman's online dictionary, "fragment" is defined as "[a] small part broken from a larger entity" (Stedmans.com, last viewed on 1/29/07). In view of this definition, it is unclear as to how a fragment of SEQ ID NO:2 can simultaneously be SEQ ID NO:2. It is suggested that applicant clarify the meaning of the claim. In the interest of advancing prosecution, the examiner has interpreted claim 9 as being limited to a polypeptide consisting of SEQ ID NO:2.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[9] Claims 8 and 10-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of he claimed invention. This is a written description rejection.

Claim 8 is drawn to a genus of isolated polypeptides comprising a fragment of SEQ ID NO:2, wherein said fragment comprises at least 500 consecutive amino acid residues of SEQ ID NO:2. Claims 10-11 are drawn to a genus of isolated polypeptides comprising a variant of a fragment of SEQ ID NO:2, wherein said fragment includes at least 500 consecutive amino acid residues of SEQ ID NO:2, optionally wherein the variant and said fragment have at least 91% sequence identity.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only a single representative species that falls within the recited genus of polypeptides, *i.e.*, SEQ ID NO:2. The specification fails to describe any additional representative species of the claimed genus of polypeptides. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." In the instant case, the recited genus of proteins encompasses species that are widely variant in both structure and function, including (but not limited to) protein variants having function other than the activity of SEQ ID NO:2, *e.g.*, non-functional polypeptides. As such, the disclosure of the single representative species of SEQ ID NO:2 is insufficient to be representative of the attributes and features of all species encompassed by the claimed genus of proteins.

Given the lack of description of a representative number of polynucleotides, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[10] Claims 8 and 10-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO:2, does not reasonably provide enablement for all polypeptides comprising fragments or variants of fragments of SEQ ID NO:2 as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation is required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). MPEP 2164.04 states, "[w]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection" and that "[t]he language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims." Accordingly, the Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: Claim 8 is so broad as to encompass all polypeptides comprising any 500 consecutive amino acids of SEQ ID NO:2 and having any biological activity or function. Claim 10 is so broad as to encompass all polypeptides comprising a variant of any 500 consecutive amino acids of SEQ ID NO:2 and having any biological activity or function. In this case, the polypeptide of claim 10 is essentially unlimited with respect to structure as there is no requirement on the allowed variation. Claim 11 limits the variation between the structure of the fragment of any 500 consecutive amino acids of SEQ ID NO:2 and the variant amino acid sequence comprised by the polypeptide to "at least 91% sequence identity," however, the function of the polypeptide is unlimited. The enablement provided by the specification is not commensurate in scope with the claims with regard to the broad scope of proteins as encompassed by the claims. In this case, the specification is enabling only for SEQ ID NO:2.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: The amino acid sequence of a polypeptide determines said polypeptide's structural and functional properties. Predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (*i.e.*, expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within a protein's sequence where modifications can be made with a reasonable expectation of success in obtaining a polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, *e.g.,* multiple substitutions. At the time of the invention, methods for isolating or generating variants of a given polypeptide were known in the art. However, neither the specification nor the state of the art at the time of the invention provided the necessary guidance for altering the polypeptide of SEQ ID NO:2 with an expectation of obtaining a polypeptide having the desired activity/utility. At the time of the invention, there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity/utility. For example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York) teaches "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... ...they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). The teachings of Branden et al. are currently exemplified by the reference of Witkowski et al. (*Biochemistry* 38:11643-11650), which teaches that only a single amino acid substitution results in conversion of the parent polypeptide's activity from a beta-ketoacyl synthase to a malonyl decarboxylase (see *e.g.*, Table 1, page 11647).

The amount of direction provided by the inventor and The existence of working examples: The specification discloses only a single working example of the claimed polypeptide, *i.e.,* SEQ ID NO:2. The prior art provides an additional working example of the claimed polypeptide. See Leung et al. (*Mol. Cell. Biol.* 18:130-140, 1998; cited at p. 1 of the IDS filed on 7/23/04), which teaches an "MRCK*α*" polypeptide (p. 132, Figure 2A). However, neither the specification nor the prior art discloses any specific guidance for altering the amino acid sequence of SEQ ID NO:2 with an expectation that the resulting variants thereof as encompassed by the claims will maintain the desired activity/utility. Further, the specification fails to provide guidance for using those polypeptides that do not maintain the activity of SEQ ID NO:2.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of isolating or generating variants of a polypeptide were known in the art at the time of the invention, it was not routine in the art to screen – by a trial and error process – for all polypeptide variants having a substantial number of modifications as encompassed by the claims for those polypeptides having the desired activity/utility.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of required experimentation, it is the examiner's position that undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention.

in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

[11] Claims 8 and 10-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Leung et al. (*Mol. Cell. Biol.* 18:130-140, 1998; cited at p. 1 of the IDS filed on 7/23/04).

Claim 8 is drawn to an isolated polypeptide comprising a fragment of SEQ ID NO:2, wherein said fragment comprises at least 500 consecutive amino acid residues of SEQ ID NO:2. Claims 10-11 are drawn to an isolated polypeptide comprising a variant of a fragment of SEQ ID NO:2, wherein said fragment includes at least 500 consecutive amino acid residues of SEQ ID NO:2, optionally wherein the variant and said fragment have at least 91% sequence identity.

The reference of Leung et al. teaches a polypeptide termed "MRCK*α*" that comprises a fragment of 1711 amino acids that comprises at least 500 consecutive amino acids of SEQ ID NO:2, *i.e.,* amino acids 1-630 and 634-1711 of SEQ ID NO:2 (p. 132, Figure 2A; see also Appendix A). The polypeptide of Leung et al. has three mismatches relative to amino acids 1-1711 of SEQ ID NO:2 at amino acids 631-633 and thus, the polypeptide of Leung et al. comprises a variant of the fragment of amino acids 1-1711 of SEQ ID NO:2, which as noted above, includes at least 500 consecutive amino acid residues of SEQ ID NO:2. Three mismatches out of the 1711 amino acids of the fragment is equivalent to an amino acid sequence identity of 99.8% between the fragment of amino acids 1-1711 of SEQ ID NO:2 and the variant of the fragment of the polypeptide of Leung et al. This anticipates claims 8 and 10-11 as written.

Examiner Comment

[12] According to MPEP 2107.II, "[i]f at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.

It is the examiner's position that the claimed invention has patentable utility. SEQ ID NO:2 has a sequence of amino acids that is 100% identical to the kinase domain of the polypeptide of Leung et al. (see Leung et al. at p. 132, Figure 2A and Appendix A) and Leung et al. discloses the MRCKα polypeptide was found to phosphorylate "several substrates, including myelin basic protein…" (p. 135, left column, bottom). Because the polypeptide of Leung et al. is shown to exhibit kinase activity, the kinase domain of the MRCKα polypeptide of Leung et al. is identical to amino acids of SEQ ID NO:2, and there is no evidence of record to suggest that SEQ ID NO:2 does not have the serine/threonine kinase activity of MRCKα, a skilled artisan would recognize that SEQ ID NO:2 more likely than not has the serine/threonine kinase activity of MRCKα. Phosphorylation of myelin basic protein is a well-recognized utility, as phosphorylated myelin basic protein is recognized in the prior art as being used as a substrate in phosphatase assays. See particularly New England Biolabs 1996/97 Catalog at p. 147. As such, a skilled artisan would recognize that SEQ ID NO:2 has utility for phosphorylating myelin basic protein.

Conclusion

[13] Status of the claims:

Claims 1-23 are pending.

Claims 1-7 and 12-23 are withdrawn from consideration.

Claims 8 and 10-11 are rejected.

Claim 9 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Monday to Friday, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656

APPENDIX A

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MRCKA_HUMAN
ID   MRCKA_HUMAN    STANDARD;      PRT;  1732 AA.
AC   Q5VT25; Q59GZ1; Q5H9N9; Q5T797; Q5VT26; Q5VT27; Q86XX2; Q86XX3;
AC   Q99646;
DT   08-NOV-2005, integrated into UniProtKB/Swiss-Prot.
DT   07-DEC-2004, sequence version 1.
DT   07-FEB-2006, entry version 15.
DE   Serine/threonine-protein kinase MRCK alpha (EC 2.7.1.37) (CDC42-
DE   binding protein kinase alpha) (Myotonic dystrophy kinase-related
DE   CDC42-binding kinase alpha) (Myotonic dystrophy protein kinase-like
DE   alpha) (MRCK alpha) (DMPK-like alpha).
GN   Name=CDC42BPA;
OS   Homo sapiens (Human).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Euarchontoglires; Primates; Catarrhini; Hominidae;
OC   Homo.
OX   NCBI_TaxID=9606;
RN   [1]
RP   NUCLEOTIDE SEQUENCE [MRNA] (ISOFORMS 3 AND 5), AND FUNCTION.
RC   TISSUE=Colon;
RX   PubMed=15723050; DOI=10.1038/ncb1230;
RA   Wilkinson S., Paterson H.F., Marshall C.J.;
RT   "Cdc42-MRCK and Rho-ROCK signalling cooperate in myosin
RT   phosphorylation and cell invasion.";
RL   Nat. Cell Biol. 7:255-261(2005).
RN   [2]
RP   NUCLEOTIDE SEQUENCE [LARGE SCALE MRNA] (ISOFORM 4).
RC   TISSUE=Brain;
RA   Totoki Y., Toyoda A., Takeda T., Sakaki Y., Tanaka A., Yokoyama S.,
RA   Ohara O., Nagase T., Kikuno F.R.;
RL   Submitted (MAR-2005) to the EMBL/GenBank/DDBJ databases.
RN   [3]
RP   NUCLEOTIDE SEQUENCE [LARGE SCALE MRNA] (ISOFORM 2).
RC   TISSUE=Testis;
RG   The German cDNA consortium;
RL   Submitted (JAN-2005) to the EMBL/GenBank/DDBJ databases.
RN   [4]
RP   NUCLEOTIDE SEQUENCE [LARGE SCALE GENOMIC DNA].
RG   Human chromosome 1 international sequencing consortium;
RL   Submitted (MAY-2005) to the EMBL/GenBank/DDBJ databases.
RN   [5]
RP   NUCLEOTIDE SEQUENCE [MRNA] OF 1-496, FUNCTION, AND TISSUE SPECIFICITY.
RC   TISSUE=Mammary gland;
RX   MEDLINE=97248557; PubMed=9092543; DOI=10.1074/jbc.272.15.10013;
RA   Zhao Y., Loyer P., Li H., Valentine V., Kidd V., Kraft A.S.;
RT   "Cloning and chromosomal location of a novel member of the myotonic
RT   dystrophy family of protein kinases.";
RL   J. Biol. Chem. 272:10013-10020(1997).
RN   [6]
RP   NUCLEOTIDE SEQUENCE [MRNA] OF 1521-1644, FUNCTION, INTERACTION WITH
RP   CDC42, AND MUTAGENESIS OF HIS-1579 AND HIS-1582.
RC   TISSUE=Brain;
RX   MEDLINE=98078670; PubMed=9418861;
RA   Leung T., Chen X.-Q., Tan I., Manser E., Lim L.;
RT   "Myotonic dystrophy kinase-related Cdc42-binding kinase acts as a
RT   Cdc42 effector in promoting cytoskeletal reorganization.";
RL   Mol. Cell. Biol. 18:130-140(1998).
RN   [7]
RP   ENZYME REGULATION, OLIGOMERIZATION, PHOSPHORYLATION SITES SER-222;
RP   SER-234 AND THR-240, AND MUTAGENESIS OF LYS-106; SER-222; SER-234;
RP   THR-240 AND THR-403.
RX   PubMed=11283256; DOI=10.1128/MCB.21.8.2767-2778.2001;
RA   Tan I., Seow K.T., Lim L., Leung T.;
RT   "Intermolecular and intramolecular interactions regulate catalytic
RT   activity of myotonic dystrophy kinase-related Cdc42-binding kinase
RT   alpha.";
RL   Mol. Cell. Biol. 21:2767-2778(2001).
CC   -!- FUNCTION: May act as a downstream effector of CDC42 in
CC       cytoskeletal reorganization. Contributes to the actomyosin
CC       contractility required for cell invasion, through the regulation
CC       of MYPT1 and thus MLC2 phosphorylation.
CC   -!- CATALYTIC ACTIVITY: ATP + a protein = ADP + a phosphoprotein.
CC   -!- COFACTOR: Magnesium.
CC   -!- ENZYME REGULATION: Maintained in an inactive, closed conformation
CC       by an interaction between the kinase domain and the negative
CC       autoregulatory C-terminal coiled-coil region. Agonist binding to
CC       the phorbol ester binding site disrupts this, releasing the kinase
CC       domain to allow N-terminus-mediated dimerization and kinase
CC       activation by transautophosphorylation.
CC   -!- SUBUNIT: Homodimer and homotetramer via the coiled coil regions.
CC       Interacts tightly with GTP-bound but not GDP-bound CDC42.
CC   -!- INTERACTION:
CC       Self; NbExp=3; IntAct=EBI-689171, EBI-689171;
CC       P60953:CDC42; NbExp=3; IntAct=EBI-689171, EBI-81752;
CC       P17081:RHOQ; NbExp=1; IntAct=EBI-689171, EBI-689202;
CC   -!- SUBCELLULAR LOCATION: Cytoplasmic. Displays a dispersed punctate
CC       distribution and concentrates along the cell periphery, especially
CC       at the leading edge and cell-cell junction. This concentration is
CC       PH-domain dependent (By similarity).
CC   -!- ALTERNATIVE PRODUCTS:
CC       Event=Alternative splicing; Named isoforms=5;
CC       Name=1;
CC         IsoId=Q5VT25-1; Sequence=Displayed;
CC         Note=No experimental confirmation available;
CC       Name=2;
CC         IsoId=Q5VT25-2; Sequence=VSP_051861, VSP_051863;
CC         Note=No experimental confirmation available;
CC       Name=3;
CC         IsoId=Q5VT25-3; Sequence=VSP_051859, VSP_051860;
CC       Name=4;
CC         IsoId=Q5VT25-4; Sequence=VSP_051862;
CC         Note=No experimental confirmation available;
CC       Name=5;
CC         IsoId=Q5VT25-5; Sequence=VSP_051860;
CC   -!- TISSUE SPECIFICITY: Abundant in the heart, brain, skeletal muscle,
CC       kidney, and pancreas, with little or no expression in the lung and
CC       liver.
CC   -!- SIMILARITY: Belongs to the Ser/Thr protein kinase family. DMPK
CC       subfamily.
CC   -!- SIMILARITY: Contains 1 CNH domain.
CC   -!- SIMILARITY: Contains 1 CRIB domain.
CC   -!- SIMILARITY: Contains 1 PH domain.
CC   -!- SIMILARITY: Contains 1 phorbol-ester/DAG-type zinc finger.
CC   -----------------------------------------------------------------------
CC   Copyrighted by the UniProt Consortium, see http://www.uniprot.org/terms
CC   Distributed under the Creative Commons Attribution-NoDerivs License
CC   -----------------------------------------------------------------------
DR   EMBL; AJ518975; CAD57745.1; -; mRNA.
DR   EMBL; AJ518976; CAD57746.1; -; mRNA.
DR   EMBL; AB208968; BAD92205.1; ALT_INIT; mRNA.
DR   EMBL; CR933723; CAI46252.1; -; mRNA.
DR   EMBL; AL353689; CAI19113.1; -; Genomic_DNA.
DR   EMBL; AL451047; CAH71184.1; -; Genomic_DNA.
DR   EMBL; AL353689; CAH71184.1; JOINED; Genomic_DNA.
DR   EMBL; AL627308; CAH71184.1; JOINED; Genomic_DNA.
DR   EMBL; AL451047; CAH71185.1; -; Genomic_DNA.
DR   EMBL; AL627308; CAH71185.1; JOINED; Genomic_DNA.
DR   EMBL; AL353689; CAH71185.1; JOINED; Genomic_DNA.
DR   EMBL; AL627308; CAH71336.1; -; Genomic_DNA.
DR   EMBL; AL353689; CAH71336.1; JOINED; Genomic_DNA.
DR   EMBL; AL451047; CAH71336.1; JOINED; Genomic_DNA.
DR   EMBL; AL627308; CAH71337.1; -; Genomic_DNA.
DR   EMBL; AL353689; CAH71337.1; JOINED; Genomic_DNA.
DR   EMBL; AL451047; CAH71337.1; JOINED; Genomic_DNA.
DR   EMBL; AL353689; CAI19108.1; -; Genomic_DNA.
DR   EMBL; AL451047; CAI19108.1; JOINED; Genomic_DNA.
DR   EMBL; AL627308; CAI19108.1; JOINED; Genomic_DNA.
DR   EMBL; AL451047; CAH71183.1; -; Genomic_DNA.
DR   EMBL; AL353689; CAH71183.1; JOINED; Genomic_DNA.
DR   EMBL; AL627308; CAH71183.1; JOINED; Genomic_DNA.
DR   EMBL; AL627308; CAH71338.1; -; Genomic_DNA.
DR   EMBL; AL353689; CAH71338.1; JOINED; Genomic_DNA.
DR   EMBL; AL451047; CAH71338.1; JOINED; Genomic_DNA.
DR   EMBL; AL353689; CAI19109.1; -; Genomic_DNA.
DR   EMBL; AL627308; CAI19109.1; JOINED; Genomic_DNA.
DR   EMBL; AL451047; CAI19109.1; JOINED; Genomic_DNA.
DR   EMBL; AL353689; CAI19110.1; -; Genomic_DNA.
DR   EMBL; AL451047; CAI19110.1; JOINED; Genomic_DNA.
DR   EMBL; AL627308; CAI19110.1; JOINED; Genomic_DNA.
DR   EMBL; U59305; AAB37126.1; -; mRNA.
DR   IntAct; Q5VT25; -.
DR   Ensembl; ENSG00000143776; Homo sapiens.
DR   HGNC; HGNC:1737; CDC42BPA.
DR   MIM; 603412; gene.
DR   InterPro; IPR001180; Citron.
DR   InterPro; IPR002219; DAG_PE_bd.
DR   InterPro; IPR003345; M_repeat.
DR   InterPro; IPR000095; PAK_box_Rho_bd.
DR   InterPro; IPR001849; PH.
DR   InterPro; IPR011993; PH_type.
DR   InterPro; IPR000961; Pkinase_C.
DR   InterPro; IPR000719; Prot_kinase.
DR   InterPro; IPR008271; Ser_thr_pkin_AS.
DR   InterPro; IPR002290; Ser_thr_pkinase.
DR   Pfam; PF00130; C1_1; 1.
DR   Pfam; PF00780; CNH; 1.
DR   Pfam; PF02370; M; 1.
DR   Pfam; PF00169; PH; 1.
DR   Pfam; PF00069; Pkinase; 1.
DR   Pfam; PF00433; Pkinase_C; 1.
DR   PRINTS; PR00008; DAGPEDOMAIN.
DR   ProDom; PD000001; Prot_kinase; 1.
DR   SMART; SM00109; C1; 1.
DR   SMART; SM00036; CNH; 1.
DR   SMART; SM00285; PBD; 1.
DR   SMART; SM00233; PH; 1.
DR   SMART; SM00133; S_TK_X; 1.
DR   SMART; SM00220; S_TKc; 1.
DR   PROSITE; PS50108; CRIB; 1.
DR   PROSITE; PS50003; PH_DOMAIN; 1.
DR   PROSITE; PS00107; PROTEIN_KINASE_ATP; 1.
DR   PROSITE; PS50011; PROTEIN_KINASE_DOM; 1.
DR   PROSITE; PS00108; PROTEIN_KINASE_ST; 1.
DR   PROSITE; PS00479; ZF_DAG_PE_1; 1.
DR   PROSITE; PS50081; ZF_DAG_PE_2; 1.
KW   Alternative splicing; ATP-binding; Coiled coil; Kinase; Magnesium;
KW   Metal-binding; Nucleotide-binding; Phorbol-ester binding;
KW   Phosphorylation; Serine/threonine-protein kinase; Transferase; Zinc;
KW   Zinc-finger.
FT   CHAIN         1   1732       Serine/threonine-protein kinase MRCK
FT                                alpha.
FT                                /FTId=PRO_0000086392.
FT   DOMAIN       77    343       Protein kinase.
FT   DOMAIN     1082   1201       PH.
FT   DOMAIN     1228   1499       CNH.
FT   DOMAIN     1571   1584       CRIB.
FT   NP_BIND      83     91       ATP (By similarity).
FT   ZN_FING    1012   1062       Phorbol-ester/DAG-type.
FT   COILED      437    820       Potential.
FT   COILED      880    943       Potential.
FT   ACT_SITE    201    201       Proton acceptor (By similarity).

  Query Match             81.3%;  Score 1408;  DB 1;  Length 1732;
  Best Local Similarity   99.8%;  Pred. No. 0;
  Matches 1708;  Conservative    0;  Mismatches    3;  Indels    0;  Gaps    0;

Qy          1 MSGEVRLRQLEQFILDGPAQTNGQCFSVETLLDILICLYDECNNSPLRREKNILEYLEWA 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MSGEVRLRQLEQFILDGPAQTNGQCFSVETLLDILICLYDECNNSPLRREKNILEYLEWA 60

Qy         61 KPFTSKVKQMRLHREDFEILKVIGRGAFGEVAVVKLKNADKVFAMKILNKWEMLKRAETA 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 KPFTSKVKQMRLHREDFEILKVIGRGAFGEVAVVKLKNADKVFAMKILNKWEMLKRAETA 120
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Qy          121 CFREERDVLVNGDNKWITTLHYAFQDDNNLYLVMDYYVGGDLLTLLSKFEDRLPEDMARF 180
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Db          121 CFREERDVLVNGDNKWITTLHYAFQDDNNLYLVMDYYVGGDLLTLLSKFEDRLPEDMARF 180

Qy          181 YLAEMVIAIDSVHQLHYVHRDIKPDNILMDMNGHIRLADFGSCLKLMEDGTVQSSVAVGT 240
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          181 YLAEMVIAIDSVHQLHYVHRDIKPDNILMDMNGHIRLADFGSCLKLMEDGTVQSSVAVGT 240

Qy          241 PDYISPEILQAMEDGKGRYGPECDWWSLGVCMYEMLYGETPFYAESLVETYGKIMNHKER 300
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          241 PDYISPEILQAMEDGKGRYGPECDWWSLGVCMYEMLYGETPFYAESLVETYGKIMNHKER 300

Qy          301 FQFPAQVTDVSENAKDLIRRLICSREHRLGQNGIEDFKKHPFFSGIDWDNIRNCEAPYIP 360
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          301 FQFPAQVTDVSENAKDLIRRLICSREHRLGQNGIEDFKKHPFFSGIDWDNIRNCEAPYIP 360

Qy          361 EVSSPTDTSNFDVDDDCLKNSETMPPPTHTAFSGHHLPFVGFTYTSSCVLSDRSCLRVTA 420
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          361 EVSSPTDTSNFDVDDDCLKNSETMPPPTHTAFSGHHLPFVGFTYTSSCVLSDRSCLRVTA 420

Qy          421 GPTSLDLDVNVQRTLDNNLATEAYERRIKRLEQEKLELSRKLQESTQTVQALQYSTVDGP 480
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          421 GPTSLDLDVNVQRTLDNNLATEAYERRIKRLEQEKLELSRKLQESTQTVQALQYSTVDGP 480

Qy          481 LTASKDLEIKNLKEEIEKLRKQVTESSHLEQQLEEANAVRQELDDAFRQIKAYEKQIKTL 540
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          481 LTASKDLEIKNLKEEIEKLRKQVTESSHLEQQLEEANAVRQELDDAFRQIKAYEKQIKTL 540

Qy          541 QQEREDLNKELVQASERLKNQSKELKDAHCQRKLAMQEFMEINERLTELHTQKQKLARHV 600
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          541 QQEREDLNKELVQASERLKNQSKELKDAHCQRKLAMQEFMEINERLTELHTQKQKLARHV 600

Qy          601 RDKEEEVDLVMQKVESLRQELRRTERAKKEVSIHTEALAAEASKDRKLREQSEHYSKQLE 660
                ||||||||||||||||||||||||||||   |||||||||||||||||||||||||||
Db          601 RDKEEEVDLVMQKVESLRQELRRTERAKKELEVHTEALAAEASKDRKLREQSEHYSKQLE 660

Qy          661 NELEGLKQKQISYSPGVCSIEHQQEITKLKTDLEKKSIFYEEELSKREGIHANEIKNLKK 720
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          661 NELEGLKQKQISYSPGVCSIEHQQEITKLKTDLEKKSIFYEEELSKREGIHANEIKNLKK 720

Qy          721 ELHDSEGQQLALNKEIMILKDKLEKTRRESQSEREEFESEFKQQYEREKVLLTEENKKLT 780
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          721 ELHDSEGQQLALNKEIMILKDKLEKTRRESQSEREEFESEFKQQYEREKVLLTEENKKLT 780

Qy          781 SELDKLTTLYENLSIHNQQLEEEVKDLADKKESVAHWEAQITEIIQWVSDEKDARGYLQA 840
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          781 SELDKLTTLYENLSIHNQQLEEEVKDLADKKESVAHWEAQITEIIQWVSDEKDARGYLQA 840

Qy          841 LASKMTEELEALRNSSLGTRATDMPWKMRRFAKLDMSARLELQSALDAEIRAKQAIQEEL 900
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          841 LASKMTEELEALRNSSLGTRATDMPWKMRRFAKLDMSARLELQSALDAEIRAKQAIQEEL 900

Qy          901 NKVKASNIITECKLKDSEKKNLELLSEIEQLIKDTEELRSEKGIEHQDSQHSFLAFLNTP 960
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          901 NKVKASNIITECKLKDSEKKNLELLSEIEQLIKDTEELRSEKGIEHQDSQHSFLAFLNTP 960

Qy          961 TDALDQFERSPSCTPASKGRRTVDSTPLSVHTPTLRKKGCPGSTGFPPKRKTHQFFVKSF 1020
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          961 TDALDQFERSPSCTPASKGRRTVDSTPLSVHTPTLRKKGCPGSTGFPPKRKTHQFFVKSF 1020

Qy         1021 TTPTKCHQCTSLMVGLIRQGCSCEVCGFSCHITCVNKAPTTCPVPPEQTKGPLGIDPQKG 1080
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         1021 TTPTKCHQCTSLMVGLIRQGCSCEVCGFSCHITCVNKAPTTCPVPPEQTKGPLGIDPQKG 1080

Qy         1081 IGTAYEGHVRIPKPAGVKKGWQRALAIVCDFKLFLYDIAEGKASQPSVVISQVIDMRDEE 1140
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         1081 IGTAYEGHVRIPKPAGVKKGWQRALAIVCDFKLFLYDIAEGKASQPSVVISQVIDMRDEE 1140

Qy         1141 FSVSSVLASDVIHASRKDIPCIFRVTASQLSASNNKCSILMLADTENEKNKWVGVLSELH 1200
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         1141 FSVSSVLASDVIHASRKDIPCIFRVTASQLSASNNKCSILMLADTENEKNKWVGVLSELH 1200
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Qy         1201 KILKKNKFRDRSVYVPKEAYDSTLPLIKTTQAAAIIDHERIALGNEEGLFVVHVTKDEII 1260
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         1201 KILKKNKFRDRSVYVPKEAYDSTLPLIKTTQAAAIIDHERIALGNEEGLFVVHVTKDEII 1260

Qy         1261 RVGDNKKIHQIELIPNDQLVAVISGRNRHVRLFPMSALDGRETDFYKLSETKGCQTVTSG 1320
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         1261 RVGDNKKIHQIELIPNDQLVAVISGRNRHVRLFPMSALDGRETDFYKLSETKGCQTVTSG 1320

Qy         1321 KVRHGALTCLCVAMKRQVLCYELFQSKTRHRKFKEIQVPYNVQWMAIFSEQLCVGFQSGF 1380
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         1321 KVRHGALTCLCVAMKRQVLCYELFQSKTRHRKFKEIQVPYNVQWMAIFSEQLCVGFQSGF 1380

Qy         1381 LRYPLNGEGNPYSMLHSNDHTLSFIAHQPMDAICAVEISSKEYLLCFNSIGIYTDCQGRR 1440
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         1381 LRYPLNGEGNPYSMLHSNDHTLSFIAHQPMDAICAVEISSKEYLLCFNSIGIYTDCQGRR 1440

Qy         1441 SRQQELMWPANPSSCCYNAPYLSVYSENAVDIFDVNSMEWIQTLPLKKVRPLNNEGSLNL 1500
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         1441 SRQQELMWPANPSSCCYNAPYLSVYSENAVDIFDVNSMEWIQTLPLKKVRPLNNEGSLNL 1500

Qy         1501 LGLETIRLIYFKNKMAEGDELVVPETSDNSRKQMVRNINNKRRYSFRVPEEERMQQRREM 1560
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         1501 LGLETIRLIYFKNKMAEGDELVVPETSDNSRKQMVRNINNKRRYSFRVPEEERMQQRREM 1560

Qy         1561 LRDPEMRNKLISNPTNFNHIAHMGPGDGIQILKDLPMNPRPQESRTVFSGSVSIPSITKS 1620
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         1561 LRDPEMRNKLISNPTNFNHIAHMGPGDGIQILKDLPMNPRPQESRTVFSGSVSIPSITKS 1620

Qy         1621 RPEPGRSMSASSGLSARSSAQNGSALKREFSGGSYSAKRQPMPSPSEGSLSSGGMDQGSD 1680
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         1621 RPEPGRSMSASSGLSARSSAQNGSALKREFSGGSYSAKRQPMPSPSEGSLSSGGMDQGSD 1680

Qy         1681 APARDFDGEDSDSPRHSTASNSSNLSSPPSP 1711
                |||||||||||||||||||||||||||||||
Db         1681 APARDFDGEDSDSPRHSTASNSSNLSSPPSP 1711
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